Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-27 are pending in the application, with 1, 7, 14-16, 19 and 27 being the independent claims. Claims 1-5, 9, 12-18, 20, 21 and 24-27 have been withdrawn. Claims 6-8, 10, 11, 19 and 23 have been amended herein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II. The Amendments

Claim 6 has been amended to make it an independent claim and to specify that the diabetes-mediating protein is one of the proteins in Tables 1 and 2. Claim 7 has been amended to depend from claim 6. Support for these amendments can be found *inter alia* in the specification in Tables 1 and 2.

Claim 8 has been amended to specify that the diabetes-mediating protein is one of the proteins having the mass spectrometry profile depicted in Figures 6-48. Support for this amendment can be found *inter alia* in Figures 6-48.

Claims 10 and 11 have been amended to make clear that the claimed proteins have the properties specified. Support for these amendments can be found, *inter alia*, in the specification at page 17, lines 8-15, and page 22, lines 32-38.

Claim 19 has been amended to recite "diabetes-related *disease*" rather than "diabetes-related *disorder*," and to specify that the diabetes-mediating protein is one of the proteins in Tables 1 or 2. Support for these amendments can be found, *inter alia*, in the specification at page 10, line 24, and in Tables 1 and 2.

Finally, claim 23 has been amended to specify that the claimed protein is selected from the group of proteins having the mass spectrometry profiles depicted in any of Figures 6-48. Support for this amendment can be found *inter alia* in Figures 6-48.

No new matter is believed to be added by these amendments, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

III. Affirmation of Election

In the Office Action, at page 3, the Examiner requests that Applicants' reply to the Office Action contain an affirmation of the election of SEQ ID NO:4 (human galectin-3) for examination. Applicants hereby affirm that election of species.

IV. Objections to the Specification

In the Office Action, at page 3, the Examiner has objected to the specification. Specifically, the Examiner has objected to the language "the presence and absence of" spanning pages 1-2 and has requested that it be changed to "the presence **or** absence of." Also, the Examiner has requested that the acronyms IEF, NEPHGE, CMV, MHC, ELISA, RIA, 2DGE and DEAE be spelled out in the first instance of use in the specification. Finally, the Examiner has objected to the term "diabetes mediating" found at page 28, line 36, and has requested that it be changed to "diabetes-mediating."

Applicants have amended the specification as requested by the Examiner. Accordingly, all grounds of objection to the specification have been addressed. Reconsideration and withdrawal of the objection is respectfully requested.

V. Objections to the Claims

In the Office Action, at page 3, the Examiner has objected to claims 6 and 8. In particular, the Examiner has objected to claim 6 on the ground that it depends from a withdrawn claim. The Examiner has requested that claim 6 be rewritten as an independent claim or as "a claim of appropriate claim dependency within the elected invention.

The Examiner has also objected to claim 8 to the extent it refers to proteins listed in Tables 1 and 2. The Examiner suggests that the proteins listed in Tables 1 and 2 can be recited in the claims per se.

Without acquiescing in the propriety of the rejection, and solely in the interest of expediting prosecution, Applicants have amended claim 6 to make it an independent claim that specifies the steps of the process of claim 1. Similarly, claim 8 has been amended to recite specific diabetes-mediating proteins from Tables 1 and 2. Accordingly, the objections to the claims have been obviated and may be withdrawn.

VI. The Rejection Under 35 U.S.C. § 101

At page 4 of the Office Action, the Examiner has rejected claims 6-8 and 10-11 under 35 USC § 101 as claiming non-statutory subject matter. Specifically, the Examiner asserts that the claims as written do not distinguish the claimed peptides or polypeptides from naturally existing products. Applicants respectfully traverse the rejection.

Claim 6 is directed to an *isolated* diabetes-mediating protein. Thus, contrary to the Examiner's assertion, claim 6 is in fact directed to a product that is altered from the form in which it is found in nature, since proteins occurring in nature are not "isolated." Further, claim 7 has been amended to recite a diabetes-mediating protein *according to claim 6*, and therefore claim 7 likewise is directed to a protein that is altered from the form in which it

exists in nature. Since claims 8 and 10-11 all depend from claim 7, they too are distinguished over proteins found in nature.

Accordingly, the grounds for rejection have been addressed and the rejection overcome. Applicants respectfully request reconsideration and withdrawal of this rejection.

VII. The Rejection Under 35 U.S.C. § 112, First Paragraph

At page 5 of the Office Action, the Examiner has rejected claims 10-11, 19, and 22 under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants respectfully traverse this rejection.

The Examiner has acknowledged that Applicants are in possession of the isolated galectin-3 polypeptide and of a process for identifying an association of galectin-3 with the diabetes state, but nevertheless contends that "Applicant is not in possession of using the galectin-3 for preventing or/and treating the diabetes." (Office Action at page 5, third paragraph.) The Examiner disputes Applicants' assertion that galectin-3 has protective activity, apparently on the ground that the specification "does not provide guidance and working examples or representative examples as to how to use this 'protective' protein to prevent against or treat diabetes disorder." (Office Action at page 5.) The Examiner

concludes that Applicants' disclosure does not reasonably establish an actual reduction to practice.

In addition, the Examiner asserts that there is no evidence that galectin-3 actually functions to prevent diabetes, as recited in claim 19 of the application. The Examiner notes (correctly) that claim 19 encompasses the administration of a diabetes-mediating protein to delay the onset of diabetes or/and ameliorate the symptoms of diabetes in a subject at risk for development of diabetes. However, he contends that "[t]he specification does [not] provide guidance and working examples as to the positive effect of the galectin-3 nor as to the negative effect of galectin-3. Thus, use of galectin-3 protein for treating or preventing diabetes is highly unpredictable." (Office Action at page 6.)

Applicants respectfully disagree with the rejection. First, Applicants note that the Examiner's rejection appears to be based not only on a perceived lack of written description, but also on a perceived lack of enablement. This is evidenced by the Examiner's reference to "working examples" and "unpredictability in the art." As noted in the "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, 'Written Description' Requirement," however, the written description requirement "is separate and distinct from the enablement requirement." (60 Fed. Reg. 1104 (January 5, 2001)).

According to the Guidelines,

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed

> invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the claimed invention.

Id.

The Examiner has the burden of proof to establish lack of written description. Indeed, "there is a 'strong presumption' that an adequate written description of the claimed invention is present when the application is filed . . . . In most cases, the statement that 'an originally filed claim is its own written description' is borne out because the claim language conveys to others of skill in the art that the applicant was 'in possession' of what is claimed." *Id.*

In the case of claims 10 and 11, the claimed subject matter is a protein. Tables 1 and 2 of the specification provide the molecular weight and pI for diabetes-mediating proteins of the invention. In addition, mass spectrometry data for the proteins of the invention are disclosed in FIGS. 6-48. Moreover, in the case of galectin-3, the complete amino acid sequence of the protein is disclosed in FIG. 5 and SEQ ID NO:4. In general, describing the chemical structure (i.e., sequence) of a polynucleotide or polypeptide is sufficient to satisfy the written description requirement. *See id.* at page 1101, right hand column. Contrary to the Examiner's assertion, the specification clearly shows an actual reduction to practice of the diabetes-mediating proteins of the invention, including galectin-3.

The Examiner's concerns about working examples showing the protective use of a protein to protect or treat diabetes and the unpredictability of treating or preventing diabetes

are more relevant to enablement of the claims rather than written description. In any event, these concerns are unfounded because the specification does in fact contain specific teachings regarding the protective effect of galectin-3 in treating diabetes. In particular, Example 8 details the expression of galectin-3 in the spontaneous development of insulin-dependent diabetes mellitus in diabetes-prone BB rats, which is an accepted animal model of the human disease. Galectin-3 expression was found to be significantly down-regulated at day 7 and at the onset of disease, whereas galectin-3 expression was increased in *in vitro* IL-1β stimulated islets and in grafts from animals which did not develop disease. *See* Example 8. Furthermore, the specification describes the expression of gal-3 in RIN cells, a cultured line of insulinoma cells, after selection for stable clones. The present inventors found that RIN cells expressing gal-3 exhibited an increased metabolic activity and proliferative rate and became more resistant to the negative effect of cytokines such as IL-1β, which is believed to be a mediator of β-cell destruction in pancreatic islets during IDDM. (*See* page 39, lines 4-9; and page 1, lines 10-21.) These data are evidence that galectin-3 is a protective diabetes-mediating protein capable of preventing or ameliorating symptoms of diabetes in humans.

The Examiner cites Pugliese, G. *et al.*, *Diabetes 49(7)*:1249-57 (2000) as suggesting a negative role of galectin-3 in the development of diabetes; however, Pugliese *et al.* are not convincing. Pugliese *et al.* merely observe that galectin-3 expression is up-regulated in the diabetic milieu. Unlike the present inventors, Pugliese *et al.* do not examine the effect of increased expression of galectin-3 on insulin producing cells, nor do they suggest that galectin-3 has either a protective or deleterious effect on the diabetes state. In fact, Pugliese

et al. acknowledge that "the impact of the altered expression of the AGE-receptor complex on the development of diabetic glomerulopathy is difficult to establish. This complication is a result of the dual function of AGE receptors mediating both AGE degradation and AGE-induced cell activation as well as not having complete knowledge of the molecular mechanisms underlying Gal-3 receptor function and its interaction with other AGE-binding proteins." Thus, Pugliese *et al.* are uncertain of the true role of galectin-3 in diabetes and they provide no reason to contradict the conclusions of the present inventors, which are based on actual experimental data.

Contrary to the Examiner's assertions, Applicants' specification contains a specific and detailed description, complete with working examples, showing the effective use of galectin-3 to prevent or treat diabetes in a well-accepted model for the human disease. Accordingly, the rejected claims are both properly described and enabled by the specification and Applicants have conceived of the invention. All grounds for rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

VIII. Rejections Under 35 U.S.C. § 112, Second Paragraph

At page 8 of the Office Action, the Examiner has rejected claims 6-7, 10-11, 19 and 22 under 35 U.S.C. 112, second paragraph as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants respectfully traverse this rejection.

The definiteness requirement "requires the language of the claim to set forth clearly the domain over which the applicant seeks exclusive rights." *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350,1358 n.2 (Fed. Cir. 1999). Furthermore, "[t]he test for whether a claim meets the definiteness requirement is 'whether one skilled in the art would understand the bounds of the claim when read in light of the specification.'" *Process Control*, 190 F.3d at 1358 n.2 (*quoting Personalized Media Communications v. Int'l Trade Comm'n*, 161 F.3d 696, 705 (Fed. Cir. 1998)). Therefore, "[i]f the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993), cert. denied, 510 U.S. 1100 (1994) (citations omitted).

The Examiner has rejected claim 6 on the ground that it "is indefinite as to how and what in the claimed protein is mediated by the process of identification." Applicants do not understand the basis for the rejection. Claim 6 as filed recites "An isolated diabetes-mediating protein identified by the process of claim 1." The term "diabetes-mediating protein" is specifically defined in the specification and the process by which such proteins are identified is clearly set forth in the specification and, in the case of amended claim 6, in the claim itself. All that is required is that the protein be identified by the specified process. Accordingly, Applicants submit that the language of claim 6 is sufficiently definite and precise.

With respect to claim 7, the examiner asserts that it "is not apparent regarding in which subject 'altered expression' of the disclosed protein occurs." (Office Action at page

8.) Applicants disagree. The claims must be interpreted in light of the corresponding specification. The specification states that "changes in protein expression are measured in a test subject suspected of developing diabetes or at risk for the development of diabetes and are expressed relative to protein expression in a normal non-diabetes control." (Page 3, lines 5-7.) Moreover, the specification indicates that the invention encompasses *in vivo* as well as *in vitro* assays for measuring altered expression. In view of the disclosure in the specification, Applicants submit that claim 7 is sufficiently clear as currently written.

The Examiner also asserts that claim 10 is unclear in the recitation of "a protective protein" because it is not clear "against what object and for what subject the protein protects." (Office Action at page 8.) Again, Applicants point out that the specification teaches that a protective protein is characterized as a protein capable of protecting *against the development of diabetes and/or delaying the onset of diabetes in a subject at risk for development of diabetes, or ameliorating symptoms of diabetes in a subject suffering from diabetes.* Further, the examiner asserts that claim 10 is unclear in the recitation of "is capable of." Without acquiescing in the propriety of the rejection, applicants have amended claim 10 to remove this language. Accordingly, the rejection has been addressed and may be withdrawn.

In the Office Action at page 9, the Examiner contends that claim 19 "is indefinite in the recitation 'diabetes-related disorder' because the recitation is not defined in the specification." Applicants have amended claim 19 to recite "diabetes-mediating disease." The specification defines "diabetes-mediating disease" as "such conditions as obesity,

circulatory deficiencies, insulin-resistance, syndrome X, diabetic retinopathy, diabetic neuropathy, and the involvement of advanced glycation end products (AGE) in neuropathy and atherosclerosis." Specification at page 10, lines 24-27. Therefore, Applicants assert that one skilled in the art, in view of the specification, would be reasonably apprized of the scope of claim 19.

In view of the above, reconsideration and withdrawal of these rejections is respectfully requested.

IX. The Rejections Under 35 U.S.C. § 102

At pages 9-13 of the Office Action, the Examiner has rejected the pending claims as anticipated by various publications. Specifically, (I) claims 6-7 and 10 have been rejected under 35 U.S.C. § 102(a) as anticipated by Ferre, T. *et al.*, *Proc. Natl. Acad. Sci. USA 93*:7225-7230 (July 1996); (II) claims 6-7, 10-11, 19 and 22 have been rejected under 35 U.S.C. § 102(b) as anticipated by Jaffa, A. A. *et al.*, *Kidney Intl. 41*:789-795 (1992) (claims 6-7 and 10), U.S. Pat. No. 5,424,286 to Eng (claims 6-7, 11, 19 and 22), Richardson, J.M. *et al.*, *J. Biol. Chem. 266(19)*:12690-12694 (1991) (claims 6-7), McLean, M.P. *et al.*, *Endocrinol. 136(8)*:3360-3368 (1995)(claims 6-7), and Elias, D. *et al.*, *Proc. Natl. Acad. Sci. USA 87*:1576-1580 (1990)(claims 6-7, 10-11, 19 and 22); and (III) claims 6-7, 11 and 19 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Pat. Nos. 5,770,355 to Brocia (claims 6-7) and U.S. Pat. No. 5,760,001 to Girten *et al.* (claims 6-7, 11 and 19).

Without acquiescing in the propriety of the rejections, and solely in the interest of expediting prosecution, Applicants have amended the claims to recite specific diabetes-mediating proteins disclosed in the application. None of the documents cited in the Office Action either teaches or suggests the specific diabetes-mediating proteins recited in the amended claims. Accordingly, the rejections have been obviated and may be withdrawn. Reconsideration and withdrawal of the rejections is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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